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Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy (Review)

Davies AN, Thompson J

Davies AN, Thompson J.
Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy.
Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD003782.
DOI: 10.1002/14651858.CD003782.pub3.

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[Intervention Review]

Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2020.

Citation: Davies AN, Thompson J. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. *Cochrane Database of Systematic Reviews* 2015, Issue 10. Art. No.: CD003782. DOI: 10.1002/14651858.CD003782.pub3.

ABSTRACT

Background

This is an updated version of the original Cochrane review on parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy (published in Issue 3, 2007). Salivary gland dysfunction is a predictable side effect of radiotherapy to the head and neck region. Pilocarpine hydrochloride (a choline ester) is licensed in many countries for the treatment of radiation-induced salivary gland dysfunction. Other parasympathomimetics have also been used 'off licence' in the treatment of this condition.

Objectives

To determine the efficacy and tolerability of parasympathomimetic drugs in the treatment of radiation-induced salivary gland dysfunction (specifically radiation-induced xerostomia).

Search methods

For this update, we ran searches of the Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 6), MEDLINE, EMBASE, and CINAHL in July 2015. We checked the reference lists of retrieved articles for additional studies, contacted experts in the field for unpublished and ongoing trials, and contacted relevant pharmaceutical companies for unpublished and ongoing trials.

Selection criteria

The selection criteria for the review were: 1) randomised controlled trials; 2) people suffering from radiation-induced salivary gland dysfunction; 3) people treated with parasympathomimetic drugs; and 4) assessable data available on primary outcome measure.

Data collection and analysis

The two review authors independently collected data from the full-text version of relevant papers including: 1) citation details; 2) participants; 3) interventions; 4) assessments; 5) outcomes (that is efficacy, tolerability); and 6) quality issues.

Due to a lack of appropriate data, we were unable to perform a meta-analysis.

Main results

In the original review, three studies, including a total of 298 participants, fulfilled the inclusion criteria. All three studies involved the use of pilocarpine hydrochloride. We have included no additional studies in the update of the review; we have excluded eight additional studies.

The data suggest that pilocarpine hydrochloride is more effective than placebo and at least as effective as artificial saliva. The response rate was 42% to 51%. The time to response was up to 12 weeks. The overall side effect rate was high, and side effects were the main

reason for withdrawal (6% to 15% of participants taking 5 mg three times a day had to withdraw). The side effects were usually the result of generalised parasympathomimetic stimulation (for example sweating, headaches, urinary frequency, vasodilatation). Response rates were not dose dependent, but side effect rates were dose dependent.

Authors' conclusions

There is limited evidence to support the use of pilocarpine hydrochloride in the treatment of radiation-induced xerostomia. Currently, there is little evidence to support the use of other parasympathomimetic drugs in the treatment of radiation-induced xerostomia. Available studies suggest that approximately half of patients will respond, but side effects can be problematic. The conclusions of the update are the same as the conclusions of the original review, since no new relevant studies have been published in the interim.

PLAIN LANGUAGE SUMMARY

Parasympathomimetic drugs for the treatment of 'dry mouth' due to radiotherapy

This updated review found there is limited evidence to support the use of pilocarpine hydrochloride in the treatment of radiation-induced salivary gland dysfunction ('dry mouth'). Salivary gland damage is a frequent and important complication of radiotherapy to the head and neck area; it causes dryness of the mouth with resultant problems with eating, talking, and local infection. The parasympathomimetic group of drugs have been used to treat radiotherapy-induced salivary gland damage.

We identified three studies that involved a total of 289 participants, and they all used the drug pilocarpine.

The review found that 42% to 51% of participants (4 to 5 in 10) responded to pilocarpine, although in some participants the response did not occur for up to 12 weeks. Pilocarpine was more effective than a placebo treatment, and at least as effective as an artificial saliva.

Side effects were common with pilocarpine (for example sweating, headache, passing urine frequently, flushing), but were usually reported to be mild; 6% to 15% (0.6 to 1.5 in 10) participants had to stop taking pilocarpine due to side effects.

The findings of this review are limited by the small number of good-quality trials that have been performed in this area. The update of this review did not find any new information on this topic.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews Issue 3, 2007 on 'Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy'.

Description of the condition

Xerostomia has been defined as "the subjective sensation of dryness of the mouth" (Sreebny 1996), whilst salivary gland hypofunction has been defined as "any objectively demonstrable reduction in either whole and/or individual gland flow rates" (Navazesh 1992). Xerostomia is usually the result of a decrease in the volume of saliva secreted. Indeed, normal participants complain of a dry mouth when their unstimulated whole salivary flow rate falls by 50% (Dawes 1987). However, xerostomia may also result from a change in the composition of saliva secreted (Pankhurst 1996). Thus, xerostomia may, or may not, be associated with salivary gland hypofunction. 'Salivary gland dysfunction' is an umbrella term for the presence of either xerostomia or salivary gland hypofunction (Davies 2005).

Salivary gland dysfunction is a predictable side effect of radiotherapy to the head and neck region (Guchelaar 1997). It develops soon after the initiation of radiotherapy treatment, progresses during treatment (and for some time after treatment), and is essentially permanent.

Description of the intervention

The treatment of salivary gland dysfunction involves the use of saliva substitutes and saliva stimulants (Davies 2005):

- Saliva substitutes: water, artificial salivas, other substances (e.g. milk). Saliva substitutes can improve xerostomia, but tend not to improve the other problems associated with salivary gland dysfunction.
- Saliva stimulants: organic acids, chewing gum, parasympathomimetics, other substances (e.g. sugar-free mints). Saliva stimulants can improve xerostomia as well as the other problems associated with salivary gland dysfunction. Moreover, studies suggest that patients find saliva stimulants more effective than saliva substitutes (Bjornstrom 1990).

Pilocarpine hydrochloride is licensed in many countries for the treatment of radiation-induced salivary gland dysfunction (Wiseman 1995). Other parasympathomimetics (that is choline esters, cholinesterase inhibitors) have also been used 'off licence' in the treatment of radiation-induced salivary gland dysfunction. This systematic review looked at the effectiveness of parasympathomimetic drugs in the treatment of salivary gland dysfunction (specifically xerostomia) due to radiotherapy.

How the intervention might work

Parasympathomimetic drugs stimulate muscarinic receptors within the salivary glands, which leads to an increase in saliva secretion.

Why it is important to do this review

Salivary gland dysfunction is associated with a variety of oral problems in this group of patients (for example oral discomfort, taste disturbance, difficulty chewing, difficulty swallowing, speech problems, dental caries, oral candidosis, other oral infections). Indeed, salivary gland dysfunction is associated with a significant impairment of quality of life in this group of patients (Chambers 2005). It has been calculated that 93% of patients experience xerostomia during head and neck radiotherapy, and that 74% to 85% of patients experience xerostomia one month to two years postradiotherapy, respectively (Jensen 2010).

OBJECTIVES

The objectives of this review were to determine the efficacy and tolerability of parasympathomimetic drugs in the treatment of radiation-induced salivary gland dysfunction (specifically radiation-induced xerostomia).

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) for the previous version of this review and the update. The trials could be of any design (for example parallel group, cross-over), and conducted in any setting (for example inpatient, outpatient). The trials could be published or unpublished, and could be written in any language.

Types of participants

We considered trials involving participants with radiation-induced salivary gland dysfunction for the previous version of this review and the update. The participants could be of any age, gender, or ethnic origin.

Types of interventions

We considered trials involving parasympathomimetic drugs (that is choline esters, cholinesterase inhibitors) for the previous version of this review and the update. The interventions could be given by any route, formulation, or dose. We considered trials of parasympathomimetic drugs versus no treatment, versus placebo, versus another treatment for salivary gland dysfunction, or versus a combination of the aforementioned options.

Types of outcome measures

Primary outcomes

The primary outcome measure of the review was xerostomia, that is the subjective sensation of dryness of the mouth.

Secondary outcomes

The secondary outcome measures of the review were:

1. salivary flow rates;
2. adverse effects;
3. other oral symptoms, e.g. oral discomfort, dysgeusia (taste disturbance), dysmasesia (difficulty chewing), dysphagia (difficulty swallowing), dysphonia (difficulty speaking);
4. other oral problems;
5. participant satisfaction;
6. quality of life; and
7. health economics.

Search methods for identification of studies

The search strategy was developed for MEDLINE and adapted for the other databases. Please see Appendix 1 for the search strategies used for this update.

Electronic searches

For this update we searched the following databases.

- Cochrane Oral Health Group Trials Register: searched July 2015.
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Register of Studies Online): searched July 2015 (Issue 6).
- MEDLINE: 2005 to July 2015.
- EMBASE: 2005 to July 2015.
- CINAHL: 2005 to July 2015.

Searching other resources

For this update, we searched the metaRegister of Controlled Trials (www.controlled-trials.com/mrct), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) for ongoing trials.

For the previous version of the review and this update, we checked the reference lists of retrieved articles for additional studies, contacted experts in the field for unpublished and ongoing trials, and contacted relevant pharmaceutical companies for unpublished and ongoing trials. We contacted authors for additional information about trials as necessary.

Data collection and analysis

Selection of studies

For the original version of the review and this update we (two review authors) independently assessed the title or abstract of each record to determine whether or not the paper was relevant to the review. If one or both review authors felt that a paper may be relevant, then we obtained the full-text version of that paper.

Subsequently, we independently assessed the full-text version of each paper to determine whether or not the study met the entry criteria for the review:

- RCT;
- participants suffering from radiation-induced salivary gland dysfunction;
- participants treated with parasympathomimetic drug;
- assessable data on primary outcome measure (xerostomia).

Data extraction and management

The two review authors independently collected data from the full-text versions of relevant papers using a data extraction form specifically designed for the review. The data collected included:

- citation details;
- details of participants;
- details of interventions;
- details of assessment;
- outcomes, i.e. efficacy, tolerability;
- quality issues.

Analysis

We were unable to perform a meta-analysis due to a lack of appropriate data. We approached the authors/sponsors (pharmaceutical companies) of relevant studies about the availability of additional data. However, the authors/sponsors (pharmaceutical companies) of these studies were either unable to provide additional data, unwilling to provide additional data, or did not respond to requests for additional data.

Assessment of risk of bias in included studies

The two review authors independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We completed a 'Risk of bias' table for each included study (RevMan 2014). We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process: random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process, which were therefore at high risk of bias (odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether the intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation, which were therefore at high risk of bias (open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding: identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved).
4. Incomplete outcome data (attrition bias due to amount, nature, or handling of incomplete outcome data).
5. Reporting bias due to selective outcome reporting.

Measures of treatment effect

If we had had appropriate dichotomous data from the studies, we would have used measures such as the risk ratio, odds ratio, risk difference, and number needed to treat to benefit; if we had had appropriate continuous data from the studies, we would have used the mean difference and standardised mean difference.

Unit of analysis issues

Two studies were parallel-group studies (Johnson 1993; LeVeque 1993), and the participants were independently randomised to

one of two groups (that is intervention or placebo); a single measurement from each participant for each outcome measure was collected for analysis. One study, Davies 1994, was a cross-over study, and the participants were randomised to an initial group (that is pilocarpine or artificial saliva), and then given the other treatment after a washout period; a single measurement for each treatment period from each participant for each outcome measure was collected for analysis.

Dealing with missing data

We contacted study authors/sponsors (pharmaceutical companies) to request missing data/data not available in the paper. No such data was forthcoming.

Assessment of heterogeneity

We were unable to obtain adequate data to carry out a meta-analysis, and so did not consider statistical heterogeneity.

Assessment of reporting biases

We employed a comprehensive search strategy and searched multiple databases in order to highlight all relevant published studies. We made efforts to identify unpublished studies, including reviewing clinical trials registers.

Data synthesis

Two review authors extracted data from the three included studies using a data extraction form specifically developed for the review. We were unable to obtain the necessary data to perform a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We were unable to obtain adequate data to carry out a meta-analysis, and so did not perform subgroup analyses.

Sensitivity analysis

We were unable to obtain adequate data to carry out a meta-analysis, and so did not perform sensitivity analyses.

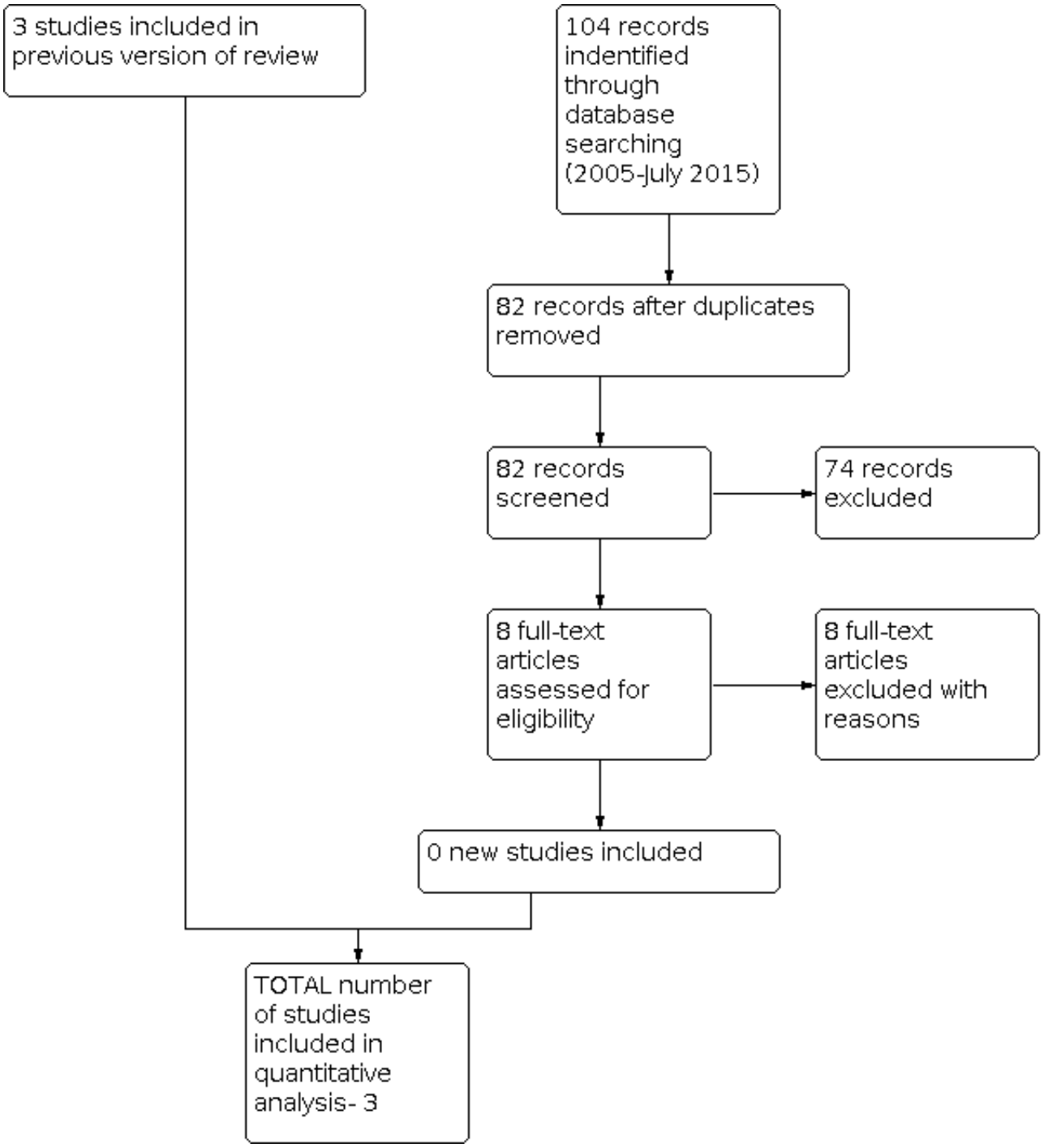
RESULTS

Description of studies

Results of the search

The original version of this review identified 248 references; in this update of the review, we identified a further 82 unique references. One study was written in Hungarian and translated by a Hungarian physician (Szabo 1985). Another study was written in Japanese and translated by a commercial company (on behalf of MGI Pharma Inc) (Matsumoto 2000). See Figure 1.

Figure 1. Study flow diagram for review update



Included studies

Only three studies fulfilled the entry criteria for the review, and all of these were included in the original version (Davies 1994; Johnson 1993; LeVeque 1993). We have summarised details of the included studies in the Characteristics of included studies table, and additional outcome data are available in Appendix 2.

All of the included studies were conducted exclusively in people with radiation-induced salivary gland dysfunction. The studies were performed in adults, and appeared to be open to people of any age, gender, or ethnic origin. All the studies were conducted in the outpatient setting. Two studies were conducted in the United States of America (Johnson 1993; LeVeque 1993), whilst the remaining study was conducted in the United Kingdom (Davies 1994).

Two studies were of parallel-group design (Johnson 1993; LeVeque 1993); participants received three months of treatment with either the active drug or the control (placebo). The remaining study was of cross-over design (Davies 1994); participants received three months with the active drug and three months with the control

(artificial saliva). There was a one-week "washout period" between the treatments.

All of the studies involved the use of pilocarpine hydrochloride. The pilocarpine was given as a tablet in two studies, Johnson 1993 and LeVeque 1993, and as a mouthwash in the remaining study (Davies 1994). The dose of pilocarpine was fixed in two studies (Davies 1994; Johnson 1993): in the Davies 1994 study, all participants received 5 mg three times a day, whilst in the Johnson 1993 study, some participants received 5 mg three times a day and others received 10 mg three times a day. By contrast, in the LeVeque 1993 study, the dose of pilocarpine was titrated, and could vary between 2.5 to 10 mg three times a day. The pilocarpine dose of was titrated on the basis of efficacy or tolerability, or both.

All of the studies assessed xerostomia: one study, Davies 1994, reported absolute changes in visual analogue scale (VAS) scores, whilst the other two studies, Johnson 1993 and LeVeque 1993, reported the number of participants with greater than 25 mm changes in VAS scores. Other assessments of efficacy included questions about the global effect of the treatment (Davies 1994; Johnson 1993; LeVeque 1993), use of other relevant treatments (Johnson 1993; LeVeque 1993), and the wish to continue with the treatment (Davies 1994).

All of the studies assessed various other oral symptoms, including oral discomfort (Johnson 1993; LeVeque 1993), dysgeusia (Davies 1994), dysphagia (Davies 1994), and dysphonia (Johnson 1993; LeVeque 1993). Only two studies measured salivary flow rates (Johnson 1993; LeVeque 1993). All of the studies assessed side effects, although only their prevalence, rather than their severity, was reported. None of the studies assessed quality-of-life data or health economics.

Two studies were conducted by a single pharmaceutical company (MGI Pharma Inc, United States of America) (Johnson 1993; LeVeque 1993), and one study was conducted by independent researchers (Davies 1994).

Excluded studies

The review authors identified 27 other references relating to unique clinical trials involving parasympathomimetic drugs in the treatment of radiation-induced salivary gland dysfunction: 19 were included in the original review, and 8 were published after the original review.

In the original review:

- one was a report of a RCT involving mixed aetiology salivary gland dysfunction; separate data for participants with radiation-induced salivary gland dysfunction was unobtainable (Fox 1991);
- one was a report of provisional results of a RCT; a final report of this study has never been published, and further information was unobtainable (Schuller 1989);
- four were reports of RCTs with inadequate data on the primary outcome (Greenspan 1987; Hamlar 1996; MacCarthy 1998; Gorsky 2004), and further information was unobtainable;
- one was a report of a RCT with inadequate data on study intervention (i.e. drug doses) (Frydrych 2002), and further information was unobtainable;
- 12 were reports of uncontrolled studies (see the Characteristics of excluded studies table).

In this update:

- five were reports of RCTs with inadequate data on the primary outcome (Abbasi 2013; Chambers 2007a; Konno 2007; Witsell 2012; Wong 2015), and further information was unobtainable;
- three were reports of uncontrolled studies (see the Characteristics of excluded studies table).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

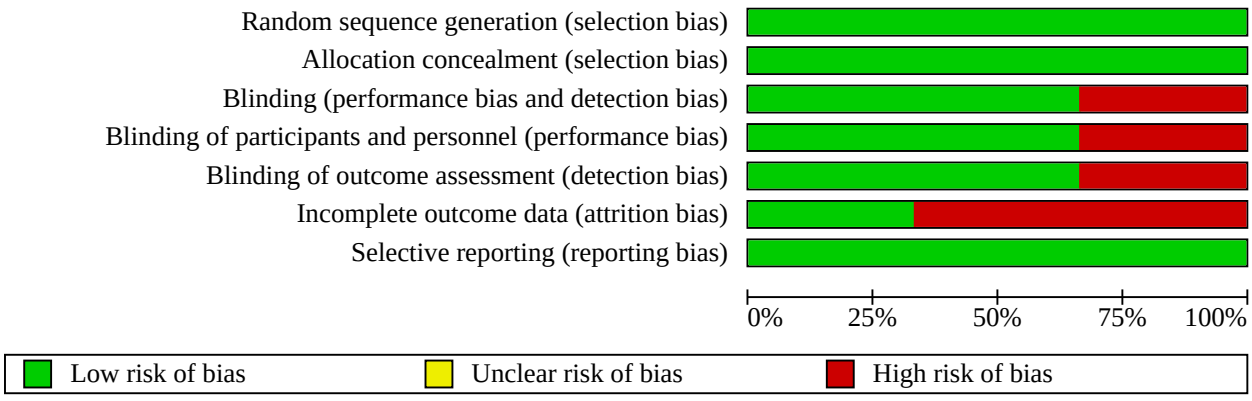
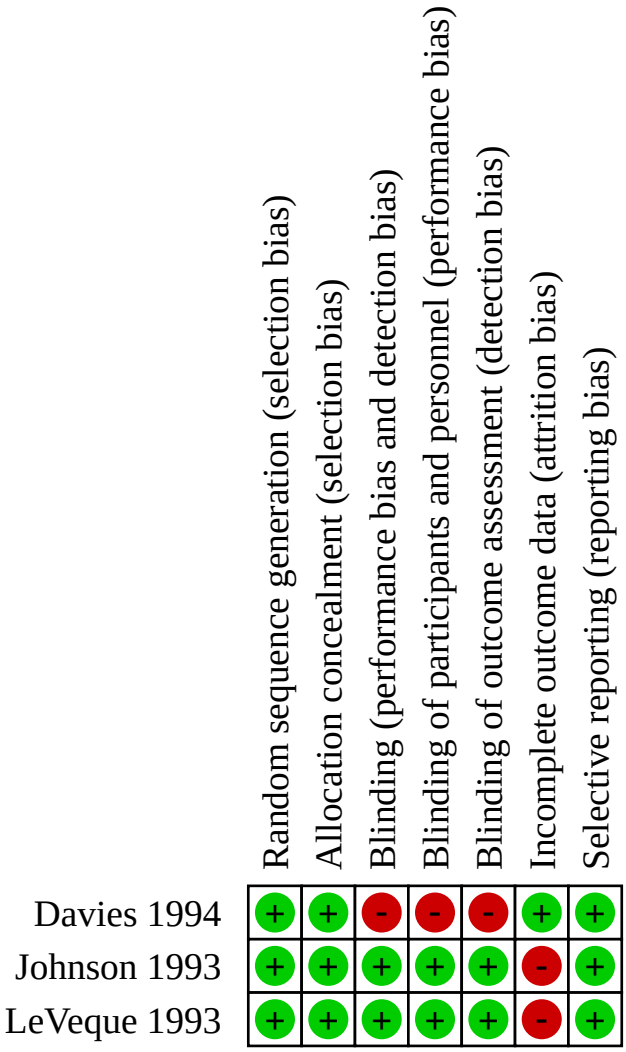


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We considered the concealment of allocation low risk of bias in all studies based on information in the published papers (Davies 1994; Johnson 1993; LeVeque 1993),

Blinding

We considered blinding high risk of bias in the study by Davies 1994, due to the fact that the intervention and control were physically different (making blinding impossible). We considered blinding low risk of bias in the Johnson 1993 and LeVeque 1993 studies.

Incomplete outcome data

We considered attrition bias low risk in the Davies 1994 study, and high risk in the other two studies (Johnson 1993; LeVeque 1993), the latter due to the fact there were more dropouts in the intervention arms due to adverse effects in these studies.

Selective reporting

We considered reporting bias low risk for all of the studies.

Other potential sources of bias

Two of the studies were commercial studies (Johnson 1993; LeVeque 1993)

Effects of interventions

We have summarised the results of the included studies in the Characteristics of included studies table.

In the Davies 1994 study, the mean improvement in VAS score with pilocarpine was 22.5 mm (100 mm scale), whilst the mean improvement in VAS score with artificial saliva was 15.2 mm. The main side effects reported with the pilocarpine were nausea (20%), sweating (15%), and lacrimation (10%). One participant withdrew from the study definitely because of side effects from the pilocarpine; another participant may have withdrawn from the study because of side effects from the pilocarpine.

In the Johnson 1993 study, a positive response (that is greater than 25 mm change in VAS score) was reported in 25% of participants receiving placebo, 51% of participants receiving pilocarpine 5 mg three times a day, and 47% of participants receiving pilocarpine 10 mg three times a day. The majority of participants responded within four weeks of the start of treatment, although some participants did not respond until eight to 12 weeks. Side effects were common, and the incidence of side effects was dose dependent. The most common side effects at the standard 5 mg three times a day dose were sweating (37%), headache (15%), urinary frequency (14%), vasodilatation (12%), dizziness (10%), dyspepsia (10%), nausea (8%), asthenia (8%), and diarrhoea (5%). Side effects were reported as being "generally mild", although 6% of participants receiving 5 mg three times a day withdrew from the study because of side effects. Twenty-nine percent of participants receiving 10 mg three times a day withdrew from the study because of side effects.

In the LeVeque 1993 study, a positive response (that is greater than 25 mm change in VAS score) was reported in 7% of participants receiving placebo, and 42% of participants receiving pilocarpine. Side effects were common, and the incidence of side effects was dose dependent. The most common side effects at the standard 5 mg three times a day dose were sweating (21%) and rhinitis (6%). Side effects were reported as being "generally mild", although 15% of participants receiving pilocarpine withdrew from the study because of side effects.

DISCUSSION

We have included no new studies in the update of the original review.

Summary of main results

Data from the original review suggest that pilocarpine hydrochloride can be effective in the management of radiation-induced xerostomia (Davies 1994; Johnson 1993; LeVeque 1993). Nevertheless, a significant number of patients do not respond to pilocarpine hydrochloride (49% to 52%) (Johnson 1993; LeVeque 1993). Furthermore, the response rate in these studies may not reflect the response rates in the general population. One of the inclusion criteria for the two main studies was "some evidence of residual salivary function" (Johnson 1993; LeVeque 1993), which is clearly not a universal finding in people with radiation-induced salivary gland dysfunction. It is reasonable to suppose that people with evidence of salivary gland functioning would be more likely to respond to pilocarpine, since such findings confirm that the salivary glands are still functioning to an extent, and so still capable of responding to a stimulant. Another important consideration is the criterion employed to define a positive response: the researchers adopted a greater than 25 mm change in VAS score, although they did not state the reasons for choosing this particular cutoff point (Johnson 1993; LeVeque 1993).

Overall, the response rates were similar for participants taking standard and higher doses (5 mg three times a day, 10 mg three times a day) in the main fixed-dose study (Johnson 1993). Nevertheless, some participants only appeared to respond to the higher doses (10 mg three times a day) in the dose titration study (LeVeque 1993). There are two possible explanations for the latter finding: a) some participants improved because of the dose increase; or b) some participants improved because of the increase in time on the drug, that is some participants had a delayed response to the drug. It is difficult to determine the importance of these two factors, although it is clear from the data that some participants do have a delayed response to the drug, that is up to 12 weeks (Johnson 1993).

The studies highlight the fact that significant numbers of patients develop side effects with pilocarpine hydrochloride. The side effects are usually related to generalised parasympathetic stimulation, and include sweating, headache, urinary frequency, and vasodilatation. The incidence of side effects appears to be related to the dose of the pilocarpine, that is the higher the dose of pilocarpine, the higher the incidence of side effects. For example, the incidence of sweating was 37% at a dose of 5 mg three times a day, but 80% at a dose of 10 mg three times a day (Johnson 1993). The severity of side effects may also be related to the dose of pilocarpine; the higher the dose of pilocarpine, the greater the incidence of withdrawals from side effects. For example, the incidence of withdrawals from side effects was 6% at a dose of 5 mg three times a day, but 29% at a dose of 10 mg three times a day (Johnson 1993). The reporting of the severity of side effects was minimal, with the authors merely stating that "adverse effects were generally mild" (Johnson 1993; LeVeque 1993). Nevertheless, the development of side effects was the predominant reason for withdrawal from the studies (Davies 1994; Johnson 1993; LeVeque 1993).

The response to pilocarpine hydrochloride is likely to depend on a number of factors, including degree of damage to the salivary glands (Guchelaar 1997), concomitant medical problems, concomitant drug treatment, and pharmacokinetic factors. For example, investigators have found an association between response to pilocarpine and levels of serum pilocarpine esterase: people with higher levels of pilocarpine esterase tended to require higher doses of pilocarpine to produce an effect and to experience fewer side effects; people with lower levels of pilocarpine esterase tended to require lower doses of pilocarpine to produce an effect and to experience more side effects (Aromdee 1996).

There is no new data in this update.

Overall completeness and applicability of evidence

All of the included studies addressed radiotherapy-induced salivary gland dysfunction, and involved the use of the parasympathomimetic drug pilocarpine. All of the studies focused on important outcomes related to this condition, that is xerostomia and related issues, and changes in salivary flow rates. The included studies are all relevant to the review question, and most importantly focus on patient-related outcomes.

Currently, there is little evidence to support the use of other parasympathomimetic drugs in the treatment of radiation-induced xerostomia. Two RCTs investigated cevimeline hydrochloride (Chambers 2007a; Witsell 2012); these trials suggest that cevimeline

may be an effective intervention (Chambers 2007a), but there is inadequate published data relating to xerostomia (and we have been unable to obtain unpublished data relating to xerostomia).

Quality of the evidence

The data suggest that pilocarpine hydrochloride is at least as effective as a mucin-based artificial saliva in the management of radiation-induced xerostomia (Davies 1994). The improvement in xerostomia was greater with pilocarpine hydrochloride, but this improvement was not statistically significant. It should be noted that this was a small study (that is 20 participants). However, the data suggest that pilocarpine hydrochloride is more effective than the mucin-based artificial saliva in the management of dysgeusia. Data from the other studies confirm that pilocarpine improves not only the xerostomia, but also the associated symptoms of salivary gland dysfunction (that is oral discomfort, dysphonia) (Johnson 1993; LeVeque 1993).

Potential biases in the review process

Due to the comprehensive search strategy and the use of multiple databases, it is very likely that we identified all relevant studies. It was not possible to obtain data from some of the studies identified in the update of this review, hence we could not include them in the review. This could have introduced bias into the review process.

Agreements and disagreements with other studies or reviews

The evidence for this update was systematically reviewed by two authors, and to our knowledge there is no disagreement with other studies or reviews.

AUTHORS' CONCLUSIONS

Implications for practice

The conclusions of the updated review are the same as the conclusions of the original review, in spite of the publication of additional RCTs.

For people with radiation-induced salivary gland dysfunction:

There is limited evidence to support the use of pilocarpine hydrochloride in the treatment of radiation-induced xerostomia. It would seem appropriate to offer patients a trial of the drug, assuming that there are no contraindications (that is uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, uncontrolled cardiorenal disease, acute iritis, pregnancy, breast-feeding) to the use of the drug.

For clinicians:

It would seem appropriate to offer patients a trial of the drug. The trial should be prolonged, since the response can be delayed (up to 12 weeks). The dose used should be 5 mg three times a day to keep side effects to a minimum, since the adverse effects are dose dependent (and the response does not appear to be dose dependent). However, many patients fail to respond to pilocarpine hydrochloride. Currently, there is little evidence to support the use of other parasympathomimetic drugs in the treatment of radiation-induced xerostomia.

For policymakers and funders:

A trial of pilocarpine is recommended for people with symptomatic radiation-induced salivary gland dysfunction, and policymakers/funders should support this option for treatment.

Implications for research

Additional studies are required to clarify the role of other parasympathomimetic drugs in the treatment of radiation-induced xerostomia. Similarly, additional studies are also required to clarify the role of other interventions in the treatment of radiation-induced xerostomia (for example saliva substitutes, other saliva stimulants). The aim of such studies should be to determine whether these other interventions have greater efficacy or tolerability, or both, as compared to pilocarpine. It is important that future studies focus on the impact of these interventions on the symptoms of salivary gland dysfunction (for example xerostomia, oral discomfort), since these are the 'outcome measures' that determine adherence or non-adherence with treatment. It is equally important that future studies assess the impact of these interventions on the important complications of salivary gland dysfunction (for example dental caries, oral candidosis).

In addition, studies are required in people who have undergone intensity-modulated radiotherapy (and other tissue-sparing techniques) as well as in people who have undergone so-called conventional radiotherapy.

ACKNOWLEDGEMENTS

The search strategy was prepared by Sylvia Bickley, who was the Trials Search Co-ordinator for the Cochrane Pain, Palliative and Supportive Care (PaPaS) Group and the Cochrane Oral Health Group. Anne Littlewood (Trials Search Co-ordinator, Cochrane Oral Health Group) and Jo Abbott (Trials Search Co-ordinator, Cochrane PaPaS Group) updated the searches for the current review. Dr Kate Shorthose was an author for the original review.

Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Davies 1994

Study characteristics	
Methods	Randomised controlled trial Cross-over design Unblinded
Participants	20 outpatients 12 male, 8 female Mean age 63 yrs (range 46 to 82 yrs) 16 carcinomas, 4 lymphomas Mean dose radiotherapy 55 Gy (range 35 to 65 Gy) Mean time since radiotherapy - not stated Inclusion criteria - not stated Exclusion criteria - not stated
Interventions	Pilocarpine mouthwash 5 mg 3 times a day Saliva Orthana spray (mucin-based artificial saliva) 2 to 3 sprays when necessary Each treatment used for 3 months (1 week washout period)
Outcomes	Primary outcome (xerostomia): Measured using participant-rated VAS (100 mm VAS, higher scores representing less xerostomia). Change in 100 mm VAS from baseline to end of treatment period. Pilocarpine - mean +22.5 mm Saliva Orthana - mean +15.2 mm Secondary outcomes: dysphagia, dysgeusia, adverse effects Change in 100 mm VAS from baseline to end of treatment period Withdrawals
Notes	Original trial data could not be traced. Data on efficacy relates to those participants who completed the study (17/20 participants). No period/carry-over effect reported. The improvement in xerostomia was not statistically significant.

Davies 1994 *(Continued)*

	The paper reports that 10/17 participants preferred the pilocarpine, 4/17 preferred the Saliva Orthana, and 3/17 had no preference; 8/17 participants wanted to continue with the pilocarpine, 3/17 wanted to continue with the Saliva Orthana, and 6/17 did not want to continue with either treatment after the trial. It is unclear what treatment 1 participant was taking when they were withdrawn from the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study's primary author reports that participants were adequately randomised to reduce risk of bias
Allocation concealment (selection bias)	Low risk	Study's primary author reports that allocation concealment was adequate to reduce risk of bias
Blinding (performance bias and detection bias)	High risk	Open study comparing an oral tablet and an oral spray
Blinding of participants and personnel (performance bias)	High risk	Open study comparing an oral tablet and an oral spray
Blinding of outcome assessment (detection bias)	High risk	Open study comparing an oral tablet and an oral spray
Incomplete outcome data (attrition bias)	Low risk	Data on efficacy relates to 17/20 participants. 17/20 participants finished the study
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes have been reported

Johnson 1993

Study characteristics

Methods	Randomised controlled trial Parallel-group design Double blind
Participants	207 outpatients 142 male, 65 female Mean age 58 yrs (range - not stated) Diagnoses - head and neck cancer Mean dose radiotherapy 62 Gy (range 40 to 75 Gy) Mean time since radiotherapy 978 days Inclusion criteria: 1. Radiotherapy dose > 40 Gy 2. Radiotherapy > 4 months previously 3. At least 1 parotid gland present 4. Clinically significant xerostomia

Johnson 1993 *(Continued)*

	5. Evidence of salivary gland functioning on examination Exclusion criteria: 1. Concurrent "clinically important uncontrolled cardiac, renal, and pulmonary disease" 2. Concurrent "other chronic diseases that could potentially interfere with the evaluation" of the drug 3. Concurrent ocular disease 4. Concurrent use of tricyclic antidepressants, antihistamines with anticholinergic effects, beta blockers, pilocarpine eye preparations
Interventions	Pilocarpine tablets 5 mg or 10 mg three times a day (fixed dose) Placebo 1 tablet three times a day Treatment period 12 weeks
Outcomes	Primary outcome (xerostomia): Measured using participant-rated VAS (100 mm VAS, higher scores representing less xerostomia) at baseline (before the start of treatment) and every 4 weeks. Participants with a > +25 mm change in 100 mm VAS from baseline to end of treatment period were classified as having responded. Secondary outcomes (oral discomfort, speaking ability, overall condition, adverse effects): Measured using participant-rated VAS (100 mm VAS) Withdrawals: Pilocarpine 5 mg - 8 (11%) participants - 4 adverse effects, 2 protocol deviation, 1 non-concordance, 1 personal reasons Pilocarpine 10 mg - 27 (39%) participants - 20 adverse effects, 3 personal reasons, 2 lack of effect, 1 protocol deviation, 1 "other" Placebo - 6 (9%) participants - 2 adverse effects, 2 lack of efficacy, 1 non-concordance, 1 personal reasons
Notes	Drug company declined to supply additional trial data. The paper reports decrease in the use of saliva substitutes/other agents in 18/69 participants using pilocarpine 5 mg, 18/52 participants using pilocarpine 10 mg, and 5/62 participants using placebo. The majority of participants responded within 4 weeks of the start of treatment, although some participants did not respond until 8 to 12 weeks. The paper reports that "adverse effects were generally mild".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned randomly with computer-generated randomisation codes with a block of six"
Allocation concealment (selection bias)	Low risk	"Patients were assigned randomly with computer-generated randomisation codes with a block of six"
Blinding (performance bias and detection bias)	Low risk	"The study was conducted in double blind fashion, and the code was not broken until the study was completed"
Blinding of participants and personnel (performance bias)	Low risk	"The study was conducted in double blind fashion, and the code was not broken until the study was completed"
Blinding of outcome assessment (detection bias)	Low risk	"The study was conducted in double blind fashion, and the code was not broken until the study was completed"

Johnson 1993 *(Continued)*

Incomplete outcome data (attrition bias)	High risk	Higher number of dropouts in intervention group compared to control group
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes have been reported

LeVeque 1993

Study characteristics	
Methods	Randomised controlled trial Parallel-group design Double blind
Participants	162 outpatients 115 male, 47 female Mean age 58 yrs (range - not stated) Diagnoses - head and neck cancer Mean dose radiotherapy 60 Gy (range not stated) Mean time since radiotherapy 914 days Inclusion criteria: 1. Radiotherapy dose > 50 Gy 2. Radiotherapy > 4 months previously 3. At least 1 parotid gland present 4. Clinically significant xerostomia 5. Evidence of salivary gland functioning on examination Exclusion criteria: 1. Diagnosis of lymphoma 2. Concurrent "clinically significant uncontrolled cardiac, renal, or pulmonary disease" 3. Concurrent "other chronic diseases that could potentially interfere with the evaluation" of the drug 4. Concurrent ocular disease 5. Concurrent use of tricyclic antidepressants, antihistamines with anticholinergic effects, beta blockers, pilocarpine eye preparations
Interventions	Pilocarpine tablets 2.5 mg, 5 mg, or 10 mg three times a day (dose titrated) Placebo 1 tablet three times a day (dose titrated) Treatment period 12 weeks
Outcomes	Primary outcome (xerostomia): Measured using participant-rated VAS (100 mm VAS, higher scores representing less xerostomia) at baseline (before the start of treatment) and every 4 weeks. Participants with a > +25 mm change in 100 mm VAS from baseline to end of treatment period were classified as having responded. Secondary outcomes (oral discomfort, speaking ability, overall condition, adverse effects): Measured using participant-rated VAS (100 mm VAS, higher scores representing less xerostomia) at baseline (before the start of treatment) and every 4 weeks. Withdrawals:

LeVeque 1993 *(Continued)*

	Pilocarpine - 12 (16%) participants - 11 adverse effects, 1 personal reasons Placebo - 18 (21%) participants - 9 adverse effects, 3 lack of effect, 3 personal reasons, 1 protocol deviation, 1 non-concordance, 1 "other"
Notes	Drug company declined to supply additional trial data. The participants did not respond to the 2.5 mg dose of pilocarpine. The paper reports decrease in use of saliva substitutes/other agents in 18/69 participants using pilocarpine and 10/77 participants using placebo. The paper reports that "adverse effects were generally mild".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated randomisation code with a block of six was used"
Allocation concealment (selection bias)	Low risk	"A computer-generated randomisation code with a block of six was used"
Blinding (performance bias and detection bias)	Low risk	"The placebo tablets used in this study were an inert, cellulose and stearic acid composition identical to the active agent in size, colour and overall appearance"
Blinding of participants and personnel (performance bias)	Low risk	"The placebo tablets used in this study were an inert, cellulose and stearic acid composition identical to the active agent in size, colour and overall appearance"
Blinding of outcome assessment (detection bias)	Low risk	"The placebo tablets used in this study were an inert, cellulose and stearic acid composition identical to the active agent in size, colour and overall appearance"
Incomplete outcome data (attrition bias)	High risk	Dropouts: 12 pilocarpine/18 control
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes have been reported

VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbasi 2013	RCT comparing oral pilocarpine and oral bromhexine. No robust data available on primary outcome (xerostomia)
Chambers 2007a	RCT comparing oral cevimeline and placebo. No robust data available on primary outcome (xerostomia)
Chambers 2007b	Uncontrolled study of oral cevimeline
Chitapanarux 2008	Uncontrolled study of oral pilocarpine

Study	Reason for exclusion
Cooper 1999	Uncontrolled study of oral pilocarpine
Epstein 1987	Uncontrolled study of oral pilocarpine together with oral antholetrithione
Epstein 1994	Uncontrolled study of oral bethanechol
Ferguson 1991	Uncontrolled study of oral pilocarpine
Fox 1991	RCT comparing oral pilocarpine and placebo. Data only available on all participants randomised to study (mixed aetiology salivary gland dysfunction)
Frydrych 2002	RCT comparing topical pilocarpine and artificial saliva. No robust data available on doses of pilocarpine used
Gorsky 2004	RCT comparing oral pilocarpine and oral bethanechol. No robust data available on primary outcome (xerostomia)
Greenspan 1987	RCT comparing oral pilocarpine and placebo. No robust data available on primary outcome (xerostomia)
Hamlar 1996	RCT comparing topical pilocarpine and placebo. No data available on primary outcome (xerostomia)
Horiot 2000	Uncontrolled study of oral pilocarpine
Jacobs 1996	Uncontrolled study of oral pilocarpine
Joensuu 1993	Uncontrolled study of oral pilocarpine and oral carbacholine
Konno 2007	RCT comparing oral pilocarpine and placebo. No robust data available on primary outcome (xerostomia)
Leek 2002	Uncontrolled study of oral pilocarpine
MacCarthy 1998	Abstract. RCT comparing oral pilocarpine and placebo. No data available on primary outcome (xerostomia)
Matsumoto 2000	Uncontrolled study of oral pilocarpine
Mosqueda-Taylor 2004	Uncontrolled study of oral pilocarpine
Nakamura 2009	Uncontrolled study of oral pilocarpine
Schuller 1989	RCT comparing oral pilocarpine and placebo. Data only available on initial participants randomised to study
Singhal 1997	Uncontrolled study of oral pilocarpine
Szabo 1985	Uncontrolled study of parenteral pilocarpine
Witsell 2012	RCT comparing oral cevimeline and placebo. No robust data available on primary outcome (xerostomia)
Wong 2015	RCT comparing oral pilocarpine and acupuncture-like transcutaneous electrical nerve stimulation. No robust data available on primary outcome (xerostomia)

RCT: randomised controlled trial

APPENDICES

Appendix 1. Search strategies for the 2015 update

CENTRAL (CRSO)

MESH DESCRIPTOR Radiotherapy

radioth*:TI,AB,KY

radiat*:TI,AB,KY

irradiat*:TI,AB,KY

#1 OR #2 OR #3 OR #4

MESH DESCRIPTOR Xerostomia

xerostomi*:TI,AB,KY

radioxerost*:TI,AB,KY

("dry mouth"):TI,AB,KY

("salivary gland hypofunction"):TI,AB,KY

("salivary gland dysfunction"):TI,AB,KY

saliv*:TI,AB,KY

#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

MESH DESCRIPTOR Parasympathomimetics

MESH DESCRIPTOR Cholinergic Agonists

MESH DESCRIPTOR Acetylcholine

MESH DESCRIPTOR Bethanechol Compounds

MESH DESCRIPTOR Bethanechol

MESH DESCRIPTOR Carbachol

MESH DESCRIPTOR Methacholine Chloride

MESH DESCRIPTOR Pilocarpine

MESH DESCRIPTOR Cholinesterase Inhibitors

MESH DESCRIPTOR Ambenonium Chloride

MESH DESCRIPTOR Edrophonium

MESH DESCRIPTOR Neostigmine

MESH DESCRIPTOR Paraoxon

MESH DESCRIPTOR Physostigmine

MESH DESCRIPTOR Pyridostigmine Bromide

parasympathomimetic*:TI,AB,KY

(choline esters):TI,AB,KY

cholinomimetics:TI,AB,KY

(aceclidine hydrochloride):TI,AB,KY

acetylcholine:TI,AB,KY

(bethanechol chloride):TI,AB,KY

carbachol:TI,AB,KY

(choline alfoscerate):TI,AB,KY

(choline alfoscerate):TI,AB,KY

(methacholine chloride):TI,AB,KY

pilocarpine:TI,AB,KY

(cholinesterase inhibitor*):TI,AB,KY

anticholinesterases:TI,AB,KY

ambenonium:TI,AB,KY

(demecarium bromide):TI,AB,KY

distigmine:TI,AB,KY

edrophonium:TI,AB,KY

(eseridine salicylate):TI,AB,KY

(eseridine salicylate):TI,AB,KY

(galantamine hydrobromide):TI,AB,KY

neostigmine:TI,AB,KY

paraoxon:TI,AB,KY

physostigmine:TI,AB,KY

pyridostigmine:TI,AB,KY

cevimeline:TI,AB,KY

#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53

#5 AND #13 AND #54

2005 TO 2015:

#55 AND #56

MEDLINE (OVID)

1. Radiotherapy/

2. radioth*.mp.

3. radiat*.mp.

4. irradiat*.mp.

5. or/1-4

6. Xerostomia/

7. xerostomi*.mp.

8. radioxerost*.mp.

9. "dry mouth".mp.

10. "salivary gland hypofunction".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11. "salivary gland dysfunction".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

12. saliv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

13. or/6-12

14. Parasympathomimetics/

15. Cholinergic Agonists/

16. Acetylcholine/

17. Bethanechol Compounds/

18. Bethanechol/

19. Carbachol/

20. Methacholine Chloride/

21. Pilocarpine/

22. Cholinesterase Inhibitors/

23. Ambenonium Chloride/

24. Edrophonium/

25. Neostigmine/

26. Paraoxon/

27. Physostigmine/

28. Pyridostigmine Bromide/

29. parasympathomimetic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

30. choline esters.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

31. cholinomimetics.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

32. aceclidine hydrochloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

33. acetylcholine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

34. bethanechol chloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

35. carbachol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

36. choline alfoscerate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

37. methacholine chloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

38. pilocarpine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

39. cholinesterase inhibitor*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

40. anticholinesterases.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

41. ambenonium.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

42. demecarium bromide.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

43. distigmine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

44. edrophonium.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

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46. galantamine hydrobromide.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

47. neostigmine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

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51. cevimeline.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

52. or/14-51

53. 5 and 13 and 52

54. randomized controlled trial.pt.

55. controlled clinical trial.pt.

56. randomized.ab.

57. placebo.ab.

58. drug therapy.fs.

59. randomly.ab.

60. trial.ab.

61. groups.ab.

62. 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61

63. exp animals/ not humans.sh.

64. 62 not 63

65. 53 and 64

66. (2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015*).ed.

67. 65 and 66

EMBASE (OVID)

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3. radiat*.mp.

4. irradiat*.mp.

5. or/1-4

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7. xerostomi*.mp.

8. radioxerost*.mp.

9. "dry mouth".mp.

10. "salivary gland hypofunction".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

11. "salivary gland dysfunction".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

12. saliv*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

13. or/6-12

14. Parasympathomimetics/

15. Cholinergic Agonists/

16. Acetylcholine/

17. Bethanechol Compounds/

18. Bethanechol/

19. Carbachol/

20. Methacholine Chloride/

21. Pilocarpine/

22. Cholinesterase Inhibitors/

23. Ambenonium Chloride/

24. Edrophonium/

25. Neostigmine/

26. Paraoxon/

27. Physostigmine/

28. Pyridostigmine Bromide/

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33. acetylcholine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

34. bethanechol chloride.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

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51. cevimeline.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

52. or/14-51

53. 5 and 13 and 52

54. random$.tw.

55. factorial$.tw.

56. crossover$.tw.

57. cross over$.tw.

58. cross-over$.tw.

59. placebo$.tw.

60. (doubl$ adj blind$).tw.

61. (singl$ adj blind$).tw.

62. assign$.tw.

63. allocat$.tw.

64. volunteer$.tw.

65. Crossover Procedure/

66. double-blind procedure.tw.

67. Randomized Controlled Trial/

68. Single Blind Procedure/

69. or/54-68

70. (animal/ or nonhuman/) not human/

71. 69 not 70

72. 53 and 71

73. (2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015*).dd.

74. 72 and 73

CINAHL (EBSCO)

S52 S50 AND S51

S51 EM 20050201-20140630

S50 S15 AND S49

S49 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48

S48 cevimeline

S47 pyridostigmine

S46 physostigmine

S45 paraoxon

S44 neostigmine

S43 (galantamine hydrobromide)

S42 (eseridine salicylate)

S41 edrophonium

S40 distigmine

S39 (demecarium bromide)

S38 ambenonium

S37 anticholinesterases

S36 (cholinesterase inhibitor*)

S35 pilocarpine

S34 (methacholine chloride)

S33 (choline alfoscerate)

S32 carbachol

S31 (bethanechol chloride)

S30 acetylcholine

S29 (aceclidine hydrochloride)

S28 cholinomimetics

S27 (choline esters)

S26 parasympathomimetic*

S25 (MH "Physostigmine")

S24 (MH "Neostigmine")

S23 (MH "Cholinesterase Inhibitors")

S22 (MH "Pilocarpine")

S21 (MH "Methacholine Chloride")

S20 (MH "Bethanechol")

S19 (MH "Bethanechol Compounds")

S18 (MH "Acetylcholine")

S17 (MH "Cholinergic Agonists")

S16 (MH "Parasympathomimetics")

S15 S5 AND S14

S14 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S13 saliv*

S12 "salivary gland dysfunction"

S11 "salivary gland hypofunction"

S10 ("dry mouth")

S9 radioxerost*

S8 radioxerost*

S7 xerostomi*

S6 (MH "Xerostomia")

S5 S1 OR S2 OR S3 OR S4

S4 irradiat*

S3 radiat*

S2 radioth*

S1 (MH "Radiotherapy")

Appendix 2. Additional outcome data

Additional outcome data

Study ID	Primary outcomes	Secondary outcomes
Davies 1994	Change in 100 mm VAS **Pilocarpine** - mean +22.5 mm **Saliva Orthana** - mean +15.2 mm	Change in 100 mm VAS **Pilocarpine** dysphagia: mean +11 mm dysgeusia: mean +18.4 mm **Saliva Orthana** dysphagia: mean +5.6 mm dysgeusia: mean +1 mm **Adverse effects:** **Pilocarpine** nausea - 4/20 (20%) sweating - 3/20 (15%) lacrimation - 2/20 (10%) headache - 1/20 (5%) oral discomfort - 1/20 (5%) GI colic - 1/20 (5%) blurred vision - 1/20 (5%) rhinorrhoea - 1/20 (5%) urinary frequency - 1/20 (5%) **Saliva Orthana** headache - 2/20 (10%)

(Continued)

	oral discomfort - 2/20 (10%) nausea - 1/20 (5%) **Withdrawals (see notes):** **Pilocarpine** - 1 (adverse effects) **Saliva Orthana** - 1 (adverse effects)
Notes	Original trial data could not be traced. Data on efficacy relates to those participants who completed the study (17/20 participants). No period/carry-over effect reported. The improvement in xerostomia was not statistically significant. The paper reports that 10/17 participants preferred the pilocarpine, 4/17 preferred the Saliva Orthana, and 3/17 had no preference; 8/17 participants wanted to continue with the pilocarpine, 3/17 wanted to continue with the Saliva Orthana, and 6/17 did not want to continue with either treatment after the trial. It is unclear what treatment 1 patient was taking when they were withdrawn from the study

Study ID	Primary outcomes	Secondary outcomes
Johnson 1993	> +25 mm change in 100 mm VAS **Pilocarpine 5 mg** - 32/63 (51%) **Pilocarpine 10 mg** - 24/51 (47%) **Placebo** - 15/59 (25%)	> +25 mm change in 100 mm VAS **Pilocarpine 5 mg** oral discomfort: 21/59 (36%) speaking ability: 21/56 (38%) “overall condition”: 37/69 (54%) **Pilocarpine 10 mg** oral discomfort: 18/45 (40%) speaking ability: 17/47 (36%) “overall condition”: 23/52 (44%) **Placebo** oral discomfort: 5/57 (9%) speaking ability: 8/54 (15%) “overall condition”: 15/62 (24%) Any increase in whole salivary flow rate after dose (at end of study) **Pilocarpine 5 mg** - 46/64 (72%) **Pilocarpine 10 mg** - 27/40 (68%) **Placebo** - 33/54 (61%) **Adverse effects:** **Pilocarpine 5 mg** sweating - 27/73 (37%) headache - 11/73 (15%)

(Continued)

urinary frequency 10/73 (14%)

vasodilatation - 9/73 (12%)

dizziness - 7/73 (10%)

dyspepsia - 7/73 (10%)

nausea - 6/73 (8%)

asthenia - 6/73 (8%)

diarrhoea - 4/73 (5%)

rhinitis - 3/73 (4%)

chills - 1/73 (1%)

Pilocarpine 10 mg

sweating - 55/69 (80%)

chills - 16/69 (23%)

nausea - 15/69 (22%)

dizziness - 13/69 (19%)

rhinitis - 13/69 (19%)

vasodilatation - 12/69 (17%)

headache - 10/69 (14%)

urinary frequency - 10/69 (14%)

asthenia - 10/69 (14%)

diarrhoea - 8/69 (12%)

dyspepsia - 7/69 (10%)

Placebo

headache - 6/65 (9%)

urinary frequency - 6/65 (9%)

sweating - 5/65 (8%)

diarrhoea - 4/65 (6%)

rhinitis - 4/65 (6%)

vasodilatation - 3/65 (5%)

dyspepsia - 3/65 (5%)

nausea - 2/65 (3%)

dizziness - 1/65 (2%)

asthenia - 1/65 (2%)

Withdrawals:

Pilocarpine 5 mg

(Continued)

		8 (11%) - 4 adverse effects, 2 protocol deviation, 1 non-concordance, 1 personal reasons **Pilocarpine 10 mg** 27 (39%) - 20 adverse effects, 3 personal reasons, 2 lack of effect, 1 protocol deviation, 1 "other" **Placebo** 6 (9%) - 2 adverse effects, 2 lack of efficacy, 1 non-concordance, 1 personal reasons
Notes	Drug company declined to supply additional data. The paper reports decrease in the use of saliva substitutes/other agents in 18/69 participants using pilocarpine 5 mg, 18/52 participants using pilocarpine 10 mg, and 5/62 participants using placebo. The majority of participants responded within 4 weeks of the start of treatment, although some participants did not respond until 8 to 12 weeks	

Study ID	Primary outcomes	Secondary outcomes
LeVeque 1993	> +25 mm change in 100 mm VAS **Pilocarpine** - 28/66 (42%) **Placebo** - 21/77 (27%)	> +25 mm change in 100 mm VAS **Pilocarpine** oral discomfort: 15/58 (26%) speaking ability: 25/59 (42%) "overall condition": 32/69 (46%) **Placebo** oral discomfort: 14/69 (20%) speaking ability: 19/71 (27%) "overall condition": 20/77 (26%) Any increase in whole salivary flow rate after dose (at end of study) **Pilocarpine** - 32/46 (70%) **Placebo** - 22/46 (48%) **Adverse effects:** **Pilocarpine 5 mg** sweating - 14/68 (21%) rhinitis - 4/68 (6%) nausea - 3/68 (4%) chills - 3/68 (4%) urinary frequency - 2/68 (3%) vasodilatation - 2/68 (3%) headache - 2/68 (3%) dizziness - 1/68 (1%)

(Continued)

	asthenia - 1/68 (1%) dyspepsia - 1/68 (1%) diarrhoea - 1/68 (1%) **Pilocarpine 10 mg** sweating - 27/52 (52%) urinary frequency - 5/52 (10%) rhinitis - 4/52 (8%) vasodilatation - 4/52 (8%) nausea - 3/52 (6%) chills - 2/52 (4%) dizziness - 2/52 (4%) asthenia - 2/52 (4%) **Placebo** sweating - 8/87 (9%) rhinitis - 7/87 (8%) headache - 6/87 (7%) urinary frequency - 5/87 (6%) dizziness - 5/87 (6%) nausea - 4/87 (5%) dyspepsia - 4/87 (5%) asthenia - 3/87 (3%) diarrhoea - 3/87 (3%) vasodilatation - 1/87 (1%) chills - 1/87 (1%) **Withdrawals:** **Pilocarpine** - 12 (16%) - 11 adverse effects, 1 personal reasons **Placebo** - 18 (21%) - 9 adverse effects, 3 lack of effect, 3 personal reasons, 1 protocol deviation, 1 non-concordance, 1 “other”
Notes	Drug company declined to supply additional trial data. The participants did not respond to the 2.5 mg dose of pilocarpine. The paper reports decrease in use of saliva substitutes/other agents in 18/69 participants using pilocarpine and 10/77 participants using placebo. The paper reports that “adverse effects were generally mild”

WHAT'S NEW

Date	Event	Description
19 October 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 3, 2007

Date	Event	Description
12 October 2015	Review declared as stable	This review will be assessed for further updating in 2020.
28 July 2015	New citation required but conclusions have not changed	No new studies were identified that met the inclusion criteria for the review
18 April 2014	New search has been performed	The review has been updated to reflect the current Cochrane guidelines for reporting reviews
27 June 2012	Amended	Contact details updated.
8 February 2011	Amended	Contact details updated.
9 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Andrew Davies: first review author; wrote protocol; reviewed studies; wrote review and update.
Jo Thompson: second review author; reviewed studies; co-wrote review and update.

DECLARATIONS OF INTEREST

Andrew Davies has no relevant conflicts of interest to declare. Jo Thompson has no relevant conflicts of interest to declare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This 2015 update reflects the changes to 'Risk of bias' assessment for included studies.

NOTES

At October 2020, we are not aware of any new potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors.

INDEX TERMS

Medical Subject Headings (MeSH)

Muscarinic Agonists [adverse effects] [*therapeutic use]; Parasympathomimetics [adverse effects] [*therapeutic use]; Pilocarpine [adverse effects] [*therapeutic use]; Radiation Injuries [*drug therapy]; Randomized Controlled Trials as Topic; Saliva, Artificial [therapeutic use]; Salivary Glands [*radiation effects]; Xerostomia [*drug therapy] [etiology]

MeSH check words

Humans